REMARKS

I. The Office Action And Amendments To The Claims

All previous rejections have been withdrawn. The Office objected to claims 1, 10, 19, 26, 32, and 34 for failing to italicize "*Treponema*." Claims 1, 4, 5, 10, 14, 19, 20, 24-26, 32, and 34 have been amended to italicize the term. Claims 1-3, 5-13, 19, 21-23, and 26-35 were newly rejected under 35 U.S.C. § 112, first paragraph, for allegedly lacking enablement. Reconsideration of the rejection is hereby requested.

II. The Rejection Under 35 U.S.C. § 112, First Paragraph, Should Be Withdrawn.

The Office rejected claims 1-3, 5-13, 19, 21-23, and 26-35 under Section 112, first paragraph, for allegedly containing subject matter which was not described in the specification in such a manner as to enable one of ordinary skill to make and/or use the invention. This rejection is respectfully traversed.

A. The specification teaches a working method of making the claimed invention.

One of ordinary skill, using the specification as a guide, could make and use the claimed carrier comprising at least one immobilized cardiolipin and at least one immobilized *Treponema*-specific antigen. Applicants describe exemplary suitable carrier materials at, e.g., page 5, lines 1-8, of the specification. Exemplary antigen concentrations and methods for immobilizing lipid and *Treponema*-specific antigens on a carrier are described in the specification at, e.g., page 4, lines 5-14, and page 10, line 3, through page 11, line 11. Materials and methods for blocking free binding sites once antigens are immobilized are described in the specification at, e.g., page 11, lines 13-19. The specification also describes materials and methods for developing nitrocellulose strips displaying antigens at, e.g., page 11, line 16, though page 12, line 6. As noted by Dr. Martin Kintrup in the Declaration under 37 C.F.R. § 1.132 dated February 4, 2009 ("first Kintrup Rule 132 declaration"), several parameters influence antigen-antibody test systems, such as pH and ion strength of the antigen containing phase, the presence of surfactants, and fixation and blocking of unsaturated binding sites. (See first Kintrup Rule 132 Declaration, paragraph 5.) The specification provides exemplary conditions for generating and developing the instantly claimed carrier, and one of ordinary skill in the art had the requisite ability to modify one or

more parameters, if needed, to produce a carrier suitable for diagnosing *Treponema* infection within the framework provided by the specification.

Moreover, the working example in the specification describes a reduction to practice of the claimed carrier. Filed herewith is a second Declaration under 37 C.F.R. § 1.132 from Dr. Kintrup ("second Kintrup Rule 132 declaration"). In the new declaration, Dr. Kintrup affirms that the procedures described at pages 10-12 of the application successfully produced a nitrocellulose test strip comprising both: (a) at least one immobilized cardiolipin and (b) at least one immobilized *Treponema*-specific antigen (see, e.g., claims 1, 10, 11, 32, and 35). (See second Kintrup Rule 132 declaration, paragraph 2.) The cardiolipin antigen was present as VDRL antigen and applied in four different concentrations on the carrier (see, e.g., claims 2, 3, and 33). (*Id.*) Four different *Treponema pallidum*-specific antigens were applied to the carrier in different positions (see, e.g., claims 4, 5, and 34). (*Id.*) A carrier also was produced comprising a serum and cut-off control, as depicted in Figure 2 (see, e.g., claims 7 and 8). (*Id.*)

Because the application teaches how to make and use the invention, the rejection alleging lack of enabling disclosure must be withdrawn.

B. Dr. Kintrup's first declaration explaining the difficulties and shortcomings of the prior art do not establish that the invention described in the application is defective.

In the first Kintrup Rule 132 declaration, Dr. Kintrup discussed art cited by the Office and described a previous failure in immobilizing both lipid and protein antigens on a single diagnostic carrier. According to the Office, based on assertions made in the declaration, one of ordinary skill in the art would not have been able to make and use the invention as claimed:

> Applicant has asserted in previous arguments (supported by the declaration) that a special means of immobilizing the cardiolipin to the solid carrier is required to prevent the cardiolipin from being solubilized under conditions which are required for the protein antigens. However, the method disclosed in the specification to create the test strips used precisely the conditions applicant has asserted will not work.

> An ethanolic solution of cardiolipin was dripped onto a test strip. The strip was subsequently treated with a solution containing 0.383% TWEEN 20, which is far greater than the 0.05% solution applicant has shown to solubilize the cardiolipin and prevent the strip from working. Applicant's entire declaration is directed to the idea that the correct concentration of detergent is required to allow the strip to function. However, the results shown in the figures of the specification and the direction given in the specification are at odds with what is taught in applicant's declaration. Therefore, there is no indication of how to properly make and use the instantly claimed carrier.
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> (Office Action, pages 5 and 6.)

Dr. Kintrup's analysis in his first Rule 132 declaration regarding immobilization of both lipid and protein antigens on a single carrier, in the context of the prior art, are not at odds with the specification's teachings. Prior to the instant invention, it was not believed that detergents, used to block nonspecific binding to proteins, could be used with lipid antigens. (See first Kintrup Rule 132 declaration, paragraphs 7 and 9.) Likewise, the coupling techniques proposed in the art for lipid immobilization are not suitable for use with proteins. (See first Kintrup Rule 132 declaration, paragraphs 7 and 9.) Applicants identified conditions whereby immobilized lipid antigen reactivity could be maintained at a level required for a diagnostic test while maintaining sensitive and selective reactivity of *Treponema* protein antigens to anti-*Treponema* antibodies on the same carrier. (See first Kintrup Rule 132 declaration, paragraph 12.) As illustrated in Figures 2, 4, and 5 of the instant application, the inventive carrier comprises both immobilized cardiolipin and immobilized *Treponema*-specific antigens suitable for detecting IgG and IgM antibodies specific for the antigens.

The Office asserts that the methods disclosed in the specification "used precisely the conditions application has asserted will not work." (Office Action, page 5.) The Office points to the utilization of 0.383% TWEEN® 20 in the specification's working example, which the Office contends is "far greater than the 0.05% solution applicant has shown [in the Rule 132 declaration] to solubilize the cardiolipin and prevent the strip from working." (Office Action, page 5.) However, the Examiner should not confuse an analysis that distinguishes prior art and identifies its shortcomings with an analysis of the working

invention described in the application. (See second Kintrup Rule 132 declaration, paragraph 3.) The success of the invention is not entirely dependent on the concentration of Tween® 20, because several assay parameters influence antigen-antibody test systems. (See second Kintrup Rule 132 declaration, paragraph 4.)

Even focusing on the blocking buffer alone, the failed experiment described in the Rule 132 declaration utilized a different buffer composition compared to the working example provided in the application. (See second Kintrup Rule 132 declaration, paragraph 4.) As described in paragraph 8 of Dr. Kintrup's first declaration, the experiment employed a phosphate buffered system (0.9% NaCl) very similar to that described in Sambri et al., *Clinical and Diagnostic Laboratory Immunology*, *8*(3), 534-539 (2001) (see page 535, lines 6 to 8), cited by the Office in the previous Section 103 rejection. (See also second Kintrup Rule 132 declaration, paragraph 4.) Like the Sambri buffer, the buffer described in the first Kintrup Rule 132 declaration comprised sodium phosphate, sodium chloride, and 0.05% TWEEN® 20. In contrast, the specification describes the use of a TRIS-buffer (3.25 g trishydroxyaminomethane and 7.5 g NaCl per liter (i.e., 0.75% NaCl)) containing TWEEN® 20 and milk powder. (*Id.*) TWEEN® 20 has different effects on immobilized antigens in the context of different buffer compositions. (*Id.*) Under the conditions taught in the specification, antigen structure and adherence to the carrier was maintained using 0.38% Tween® 20, as illustrated by Figures 2, 4, and 5 of the instant application, while the conditions disclosed in the cited art solubilized lipid antigens. (*Id.*) Dr. Kintrup's comments in the first Rule 132 declaration regarding detergents are not contrary to the teachings of the specification, which enables the full scope of the pending claims.

In the first Rule 132 declaration, Dr. Kintrup also commented that the method of adhering cardiolipin to a substrate disclosed in Pedersen et al., *J. Clin. Microbiol.*, *25*(9): 1711-1716 (1987) is not suitable for use with protein antigens. (See first Kintrup Rule 132 declaration, paragraph 10.) At page 5 of the Office Action, the Office noted that the specification teaches dripping an ethanolic solution of cardiolipin onto the test strip. The Pedersen reference teaches that polyvinyl chloride microtiter plates were *coated* with an ethanol solution containing VDRL antigen, and the ethanol was evaporated overnight. (See page 1712, column 1, paragraph 3; second Kintrup Rule 132 declaration, paragraph 5.)

Coating a carrier with ethanol would disrupt protein antigens, rendering a carrier comprising both cardiolipin and a *Treponema*-specific antigen unable to detect anti-*Treponema* antibodies. (See second Kintrup Rule 132 declaration, paragraph 5.) In contrast, the working example teaches dripping/dotting a VDRL antigen solution onto discrete locations on the carrier. (See specification at, e.g., page 11, lines 5-11; second Kintrup Rule 132 declaration, paragraph 6.) Thus, an ethanolic solution is physically removed from protein antigens, which ensures that protein antigens remain intact. Indeed, as illustrated in Figures 2, 4, and 5, dripping an ethanolic solution containing lipid antigen onto first discrete location(s)/spots(s) on a carrier did not disrupt protein antigens immobilized on second discrete location(s)/spot(s) on the same carrier. (See second Kintrup Rule 132 declaration, paragraph 6.) Dripping solution also minimizes damage to a nitrocellulose carrier. (*Id.*) In addition, the instant application teaches diluting a VDRL antigen composition containing ethanol in phosphate-buffered saline. (*Id.*) The amount of ethanol in the diluted VDRL antigen composition in the instant working example ranged from 0.8% to 50% (v/v), which minimized ethanol-related damage to the nitrocellulose. (*Id.*)

The instant specification provides sufficient guidance to allow one of ordinary skill in the art to make and use the claimed carrier without undue experimentation. Dr. Kintrup's first Rule 132 declaration does not contradict the teachings of the specification by establishing that previously disclosed methods for immobilizing a single antigen on a carrier are unsuitable for generating the presently claimed carrier comprising both lipid and *Treponema*-specific antigens. Accordingly, the Section 112, first paragraph, rejection should be withdrawn.

III. Applicants Request Reconsideration Of The Finding Of Lack Of Unity.

A number of claims were previously withdrawn from reconsideration based on allegations of lack of unity, which Applicants traversed. The Office acknowledged in the Office Action that the claims under examination were free of the art. Accordingly, Applicants request that claims that share unity with the claims under examination be examined on the merits.

IV. Conclusion

The application is considered to be in good and proper form for allowance, and the examiner is respectfully requested to pass this application to issue. The Examiner is invited to contact the undersigned attorney by telephone if there are issues or questions that might be efficiently resolved in that manner.

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Respectfully submitted,

By _____

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